Synthesis of Biodegradable Copolymers with the Use of Low Toxic Zirconium Compounds. 1. Copolymerization of Glycolide with L-Lactide Initiated by Zr(Acac)$_4$

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ABSTRACT: The paper describes a new method of copolymerization of glycolide with L-lactide with the use of a low toxic compound—Zr(acac)$_4$—as initiator at a temperature of 100 up to 150 °C. Copolymerization at 150 °C is very fast and reached nearly 100% yield. The values of the copolymerization coefficients were estimated as $r_G = 3.3$ and $r_L = 0.5$. The process of chain propagation was also examined, and a significant influence of transesterification on the final structure of copolymer was observed. The microstructure of the chain was determined by NMR spectroscopy. It was found that more segmental structure had been formed as compared with the structure of the copolymer obtained in copolymerization initiated by tin compounds. This structure influences thermomechanical properties of the copolymers. The crystallinity of copolymers obtained is higher than that of the formed in the presence of Sn(oct)$_2$. One of their most characteristic features concerned their good mechanical properties, in many cases better than those of adequate copolymers obtained with the use of tin compounds as initiators.

Introduction

Polyglycolide and its copolymers with lactide, due to their biocompatibility and relatively good mechanical properties, are more and more often applied in medical practice as very good materials for biodegradable implants employed both in bone surgery in the form of screws, plates, and surgical nails[1] and in treating injuries of some internal organs.[2] Glycolide copolymers with lactide are also widely utilized in controlled drug release as carriers in the forms of microspheres filled with drugs.[3] These copolymers are known as commercial materials (Dexon, Vicryl). Their synthesis is carried out generally with the use of tin compounds as initiators.[4,5] However, complete elimination of highly toxic tin compounds from the polymer is practically impossible.[6] As a result, tin compounds are slowly penetrating into the patient's blood circulation. It is known that these compounds even in trace amounts are especially dangerous for small children and endanger proper functioning of tissues sensitive to toxication (e.g., brain tissue, nerve tissue).[7] To avoid the side effects several attempts have been undertaken with the use of less toxic initiators, mainly zinc[8,9] and calcium.[10]

Unfortunately, with the exception of materials obtained in copolymerization initiated by zinc chloride, no other copolymers possessing sufficiently high molecular masses were observed to yield materials of satisfactory mechanical properties, which are needed in the case of surgical applications. Zirconium compounds seem to be interesting as initiators of biodegradable polymer syntheses because of their low toxicity. In many countries, they are allowed to be used in drugs and cosmetics (e.g., in the USA by the FDA[7]). So far, these compounds have not been widely used as polymerization initiators of oxacyclic compounds. Zirconium(IV) *n*-propoxide has been used for polymerization of L-lactide.[11] This compound[12] as well as zirconocene[13] have been applied in polymerization of ϵ-caprolactone.

The initiator used by us is zirconium(IV) acetylacetonate, which ehibits relatively low toxicity; it is on average from 10 to 20 times less toxic than comparable tin compounds,[7] for which even a small amount (considerably less than lethal dose) shows neurotoxicity[14] and DNA damage.[15]

It was shown in our previous communication that with the use of Zr(acac)$_4$ it is possible to obtain glycolide copolymers with L-lactide and ϵ-caprolactone having high molecular masses.[16]

In this paper, the results of investigations on glycolide copolymerization with L-lactide concerned with the influence of the copolymer composition and the reaction temperature on microstructure and mechanical properties of the obtained copolymers are presented. The findings were compared with the ones derived from polymerization initiated by Sn(oct)$_2$. In order to test the microstructure of the obtained copolymers, the NMR spectroscopy method described in our earlier work was employed.[17] This method was also applied for determination of the chain propagation process leading to the copolymer and for transesterification reactions related to this process in particular. Transesterification processes of lactide were also investigated based on measurements of molecular weight distribution.[18]

Some our earlier papers concerned with lactide copolymerization with ϵ-caprolactone differentiate the first and the second mode of transesterification.[19,20] Transesterification of the first mode takes place during intermolecular exchange of lactydyl (−LL−) and glycolydyl (−GG−) units or their multiple. In the case of transesterification of the second mode lactidyl and glycolidyl groups undergo bond cleavage, which leads to the formation of −GLG− or LGL− sequences, as well as −GLLLG− and −LGGGL− ones, and other sequences with odd numbers of lactyl (L) and glycolyl (G) units in microblocks.[17]

In the previous paper,[17] the coefficient of transesterification of the second mode was introduced for glycolyl blocks as

$$T_{II}[\mathrm{LGL}] = [\mathrm{LGL}]/[\mathrm{LGL}]_R \qquad (1)$$

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Table 1[a]

no.	initiator (temp)	N_{GG} (%)	time (h)	convn (%)	F_{GG} (%)	M_v (M_n) × 10^{-3}	l_{GG}	l_{LL}	T_{II}[GLG]	T_{II}[LGL]
1	Zr(acac)$_4$ (150 °C)	100	48	92	100	>40		0		
2	Zr(acac)$_4$ (100 °C)	80	72	97	82	280	6.7	1.5	1.0	0.1
2A	Zr(acac)$_4$ (150 °C)	80	48	≈100	80	120	4.4	1.1	3.5	0.5
2B	Sn(oct)$_2$ (100 °C)	80	72	98	81	119	4.7	1.2	1.8	0.4
3	Zr(acac)$_4$ (100 °C)	50	120	≈100	50	140	4.0	4.0	0.7	0.5
3A	Zr(acac)$_4$ (150 °C)	50	24	≈100	50	120	3.5	3.5	1.4	0.8
3B	Sn(oct)$_2$ (100 °C)	50	120	≈100	50	115	2.8	2.8	1.7	0.7
4	Zr(acac)$_4$ (100 °C)	20	120	≈100	20	135 (90); $D = 1.9$	3.1	12.4	1.1	0.4
5	Zr(acac)$_4$ (100 °C)	15	120	≈100	15	120 (85); $D = 1.9$	2.6	14.7	1.0	0.3
5A	Zr(acac)$_4$ (150 °C)	15	48	≈100	15	100 (68); $D = 1.8$	1.6	9.1	1.1	0.4
5B	Sn(oct)$_2$ (100 °C)	15	48	≈100	15	110 (70); $D = 1.9$	1.5	8.5	1.3	0.3

[a] Key: Polymerization in bulk, mole ratio of initiator to monomer, 1.2×10^{-3}; N_{GG}, feed mole fraction of glycolide (molar percentage); F_{GG}, contents of glycolide in copolymer (molar percentage); convn, total conversion of reaction; M_v, viscosity-average molecular weight; M_n, number-average molecular weight; D, molecular weight distribution; l_{gg} or l_{LL}, average length of glycolidyl or lactydyl blocks in copolymer chains; T_{II}[GLG], yield of the second mode of transesterification (sequences GLG); T_{II}[LGL], yield of the second mode of transesterification (sequences LGL).

where [LGL] is the actual amount of sequences of the given type in the copolymer and $[LGL]_R$ is the amount of sequences of the given type calculated according to Bernoulian statistics

$$[\mathrm{LGL}]_R = k/(k+1)^3 \quad \text{where } k = [\mathrm{G}]/[\mathrm{L}] \tag{2}$$

In this paper, the coefficient of transesterification of the second mode for lactidyl blocks was introduced by analogy accordingly to equations described in ref 20

$$T_{II}[\mathrm{GLG}] = [\mathrm{GLG}]/[\mathrm{GLG}]_R \tag{3}$$

where

$$[\mathrm{GLG}]_R = k^2/(k+1)^3 \tag{4}$$

The value of T_{II} is close to one (according to equations (1) and (2)) when the contribution of glycolyl and lactyl units in the chain is close to Bernoulian statistics. The value of T_{II} can be higher than 1 when longer alternative sequences of −GLGLGL− type are propagated in copolymers.

Experimental Section

Monomers and Initiators. Glycolide (Purac) and L-lactide (Purac,) were purified by recrystallization from dry ethyl acetate and dried in a vacuum oven at room temperature. Zirconium(IV) acetylacetonate (Aldrich Corp.) and stannous 2-ethylhexanoate (Sn(oct)$_2$) (Sigma Chem. Co.) were used as received.

Copolymerization Procedure. Copolymerizations of glycolide with lactide were performed in bulk at moderate temperatures in the region 100−150 °C by a conventional method using a vacuum line for degassing and sealing of the ampules.

When the copolymerization was carried out at 100 °C for an initial content of glycolide of more than 50 mol %, the reaction mixture was initially heterogenic. The obtained copolymers were ground and shaken with methyl alcohol in order to remove unreacted monomers and then dried in a vacuum at 50 °C.

Measurements. The viscosity of the obtained copolymers was determined in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at 25 °C using the Ubbelohde viscometer. The concentration of the solution was 2 g/dm^3. Intrinsic viscosity was calculated from measurements of relative viscosity on the basis of the single point method of Salomon and Ciuta.[21] The usefulness of this method was demonstrated previously for this type of copolymers.[22]

Average viscosity molecular weights, for glycolide L-lactide copolymers, were calculated using Kenley's equation:[22] $[\eta] = (1.67 \times 10^{-4})M_v^{0.794}$.

The molecular weights and polydispersity indices of copolymers, which were soluble in chloroform, were determined by a liquid chromatography method using a Waters ALC/GPC 3m apparatus (polystyrene standards) and by gel permeation chromatography with the aid of a Spectra Physics SP 8800 chromatograph (chloroform was used as the eluent, flow rate = 1 mL/min, Styragel columns 104, 103 and 500A, Shoedex SE 61 detector).

The ^{1}H NMR spectra of the copolymers were recorded at 300 MHz using a Varian Unity Inowa spectrometer and a 5 mm sample tube. Dried DMSO-d_6 was used as solvent. The spectra were obtained at 100 °C with 32 scans, 3.74 s acquisition time, and 7 μs pulse width.

The ^{13}C NMR spectra (75 MHz) were acquired on Varian Unity Inowa spectrometer using 5 mm sample tubes and dried DMSO-d_6, measurement temperature 100 °C, 3000 scans, acquisition time 1.8 s, pulse width 9 μs, and delay of 3 s between pulses.

The conversion of the reaction was determined by weighing washed and dried copolymers and by NMR spectroscopy.

The copolymer compositions, chain microstructure, and transesterification processes were defined by means of ^{1}H and ^{13}C NMR spectroscopy measurements.[17]

Thermal properties, such as glass transition temperatures and heats of crystallization or melting, were studied by differential scanning calorimeter using a DSC Du Pont 1090B apparatus calibrated with gallium and indium. The thermogravimetric measurements were conducted on a Q-1500 MOM Budapest apparatus in nitrogen atmosphere at a heating rate of 10 °C/min.

Determination of Mechanical Properties. The following samples were prepared for testing of mechanical properties:

(1) Samples for compressive strength tests. Material was melted in a closed cylindrical ampule in argon atmosphere, and then, after cooling, the casting cylinder was taken out and cut into smaller samples.

(2) Samples for tensile strength tests. The samples were cut out from disks molded on laboratory hydraulic press. Molding temperature depended on the kind of copolymer and varied from 150 to 190 °C. All samples were conditioned in the air at 23 °C for 4 days.

(3) Compressive strength testing. Cylindrical samples (30 mm high) with diameter of 12 mm were tested at 20 °C using an Instron 2402 apparatus with a cross-head speed of 2 mm per minute.

(4) Tensile strength testing and Young's modulus determination. Samples 120 mm long, 10 mm wide and 3 mm high were tested at 20 °C using an Instron 2402 apparatus with the same speed.

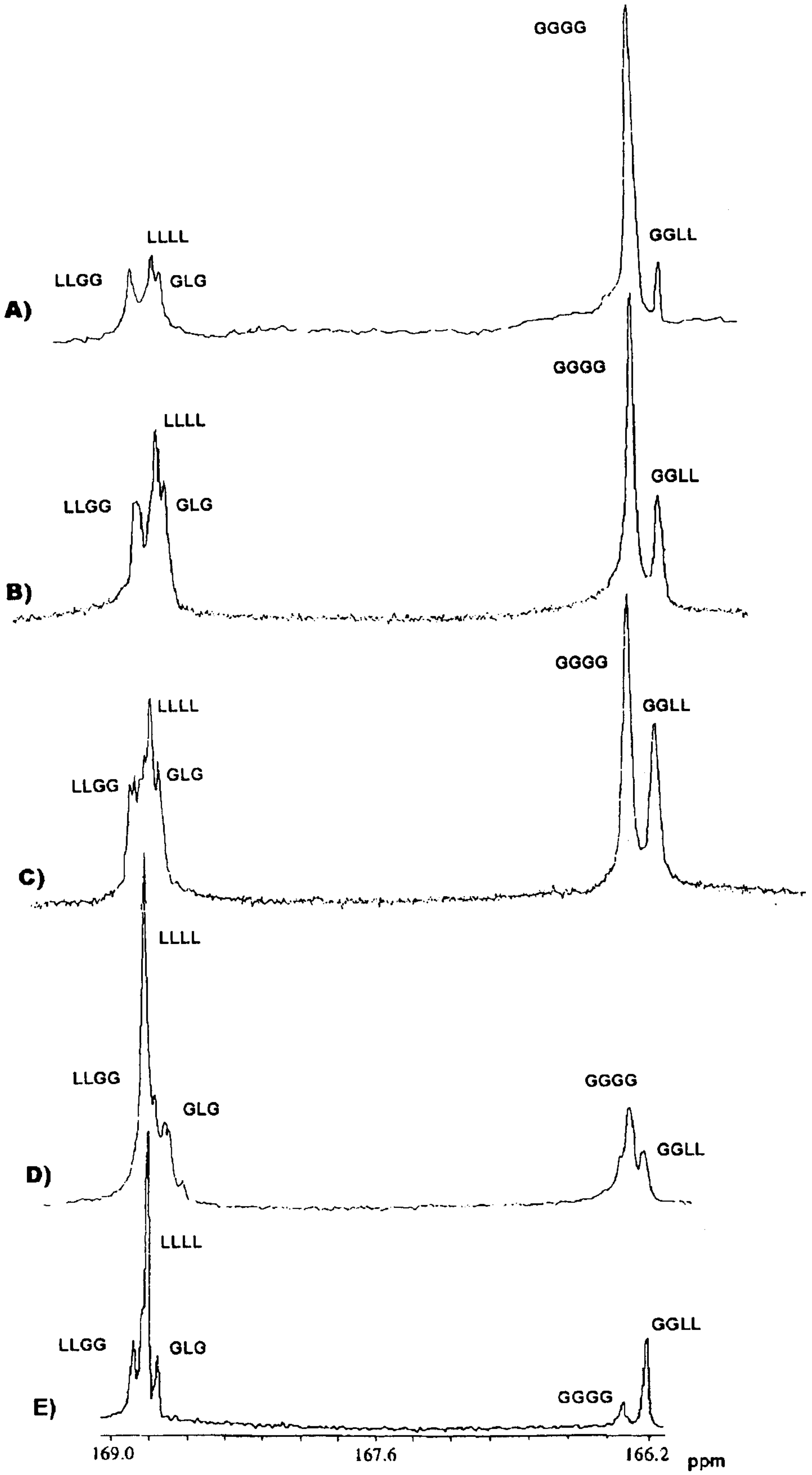

Figure 1. ^{13}C NMR spectra of poly(glycolide-*co*-L-lactide) obtained at 100 °C (carbonyl region): (A) 80 mol % of glycolide, initiator Zr(acac)$_4$ (Table 1, position 2); (B) 50 mol % of glycolide, initiator Zr(acac)$_4$ (Table 1, position 3); (C) 50 mol % of glycolide, initiator Sn(oct)$_2$ (Table 1, position 3B); (D) 15 mol % of glycolide, initiator Zr(acac)$_4$ (Table 1, position 5); (E) 15 mol % of glycolide, initiator Sn(oct)$_2$ (Table 1, position 5B).

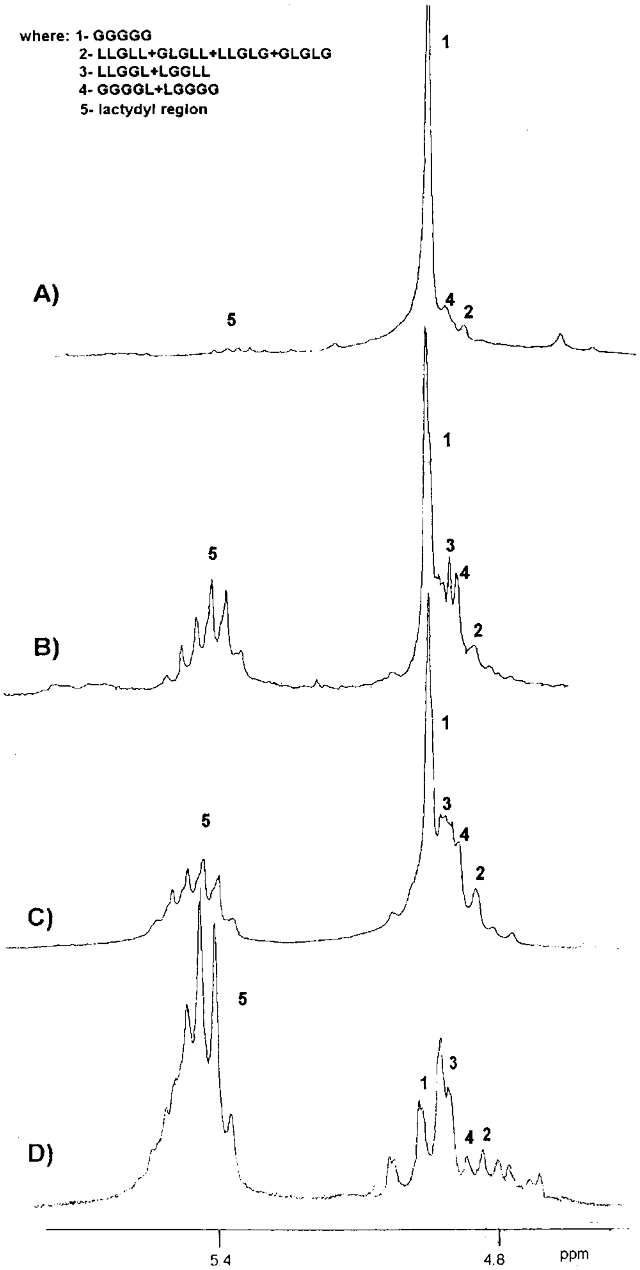

Figure 2. ^{1}H NMR spectra of poly(glycolide-*co*-L-lactide) obtained at 100 °C: (A) 80 mol % of glycolide, initiator Zr(acac)$_4$ (Table 1, position 2); (B) 50 mol % of glycolide, initiator Zr(acac)$_4$ (Table 1, position 3); (C) 50 mol % of glycolide, initiator Sn(oct)$_2$ (Table 1, position 3B); (D) 15 mol % of glycolide, initiator Zr(acac)$_4$ (Table 1, position 5).

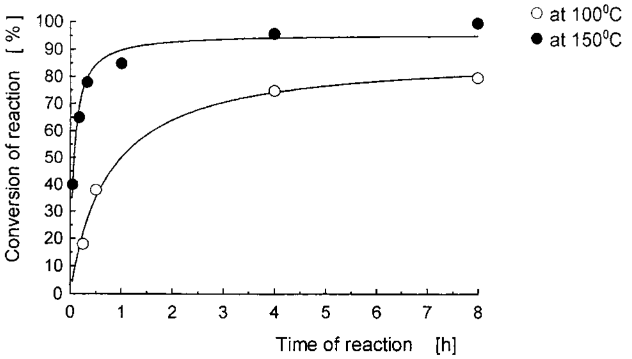

Figure 3. Conversion as a function of copolymerization time. Feed mole fraction of glycolide and lactide = 50%.

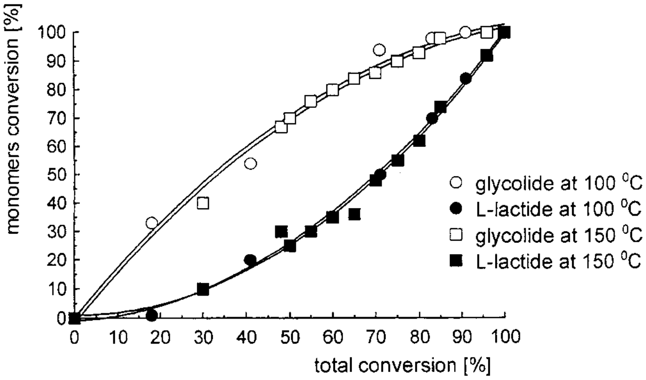

Figure 4. Dependence of the conversion L-lactide and glycolide on the total conversion of the reaction. Feed mole fraction of glycolide and lactide = 50%.

Results and Discussion

1. Results of Copolymerization. The results of polymerization of glycolide and its copolymerization with L-lactide carried out in the presence of zirconium acetylacetonate, are presented in Table 1. Some data concerning synthesis of copolymers with tin octoate are added for comparison. Both polymerization of glycolide and its copolymerization with L-lactide reached a conversion of nearly 100%. A polyglycolide of a high molecular weight was obtained. Its insolubility in hexafluoro-2-propanol at room temperature (a polyglycolide with M_v < 40 000 is soluble in such a solvent under identical conditions[23]) as well as its thermogram DSC (Figure 8A) characteristic for high molecular weight polyglycolide[24] supports this fact. The copolymers possessed high molecular weights, higher than the ones determined for the copolymers obtained in copolymerization initiated by tin octoate (Table 1, positions 2,2B and 3,3B). For copolymers soluble in THF polydispersity coefficients and molecular masses were determined by GPC. They were a bit lower than the ones reported for analogous copolymers by Gilding[5] for the reactions initiated by tin octoate ($M_w/M_n \approx 2.3-2.4$).

On the basis of the results depicted in Table 1, one can notice that average lengths of glycolidyl and lactidyl microblocks of copolymers obtained in the presence of Zr(acac)$_4$ are higher than those observed for the analogous copolymers obtained in the reactions initiated by Sn(oct)$_2$ (Table 1, positions 2,2B and 3,3B). The lengths of microblocks were calculated based on NMR spectra as shown in Figures 1 and 2.

In the ^{13}C NMR spectrum, a signal connected with the presence of a −GLG− type sequence was observed, which could originate only from intermolecular transesterification of the second mode of lactidyl groups −LL− (Figure 1). The coefficient of the second mode of lactidyl group transesteryfication (T_{II}[GLG]), calculated on the basis of this signal, was higher than 1.

It suggests the existence of longer segments of the −GLGLGLG− type in the polymer chain. It is interesting that in the case of a copolymer with low glycolide content, obtained with the use of Zr(acac)$_4$, practically no −LLGG− type sequences were observed in its chain (Figure 1D). Besides long lactidyl blocks (−LLLL−) and shorter glycolidyl ones (−GGGG−), there were linking segments which contained −GLGL− sequences.

Comparing the ^{1}H NMR spectra of copolymers with different chemical compositions, quite a distinct signal connected with the presence of the sequences containing the −LGL− segment, which could originate only from

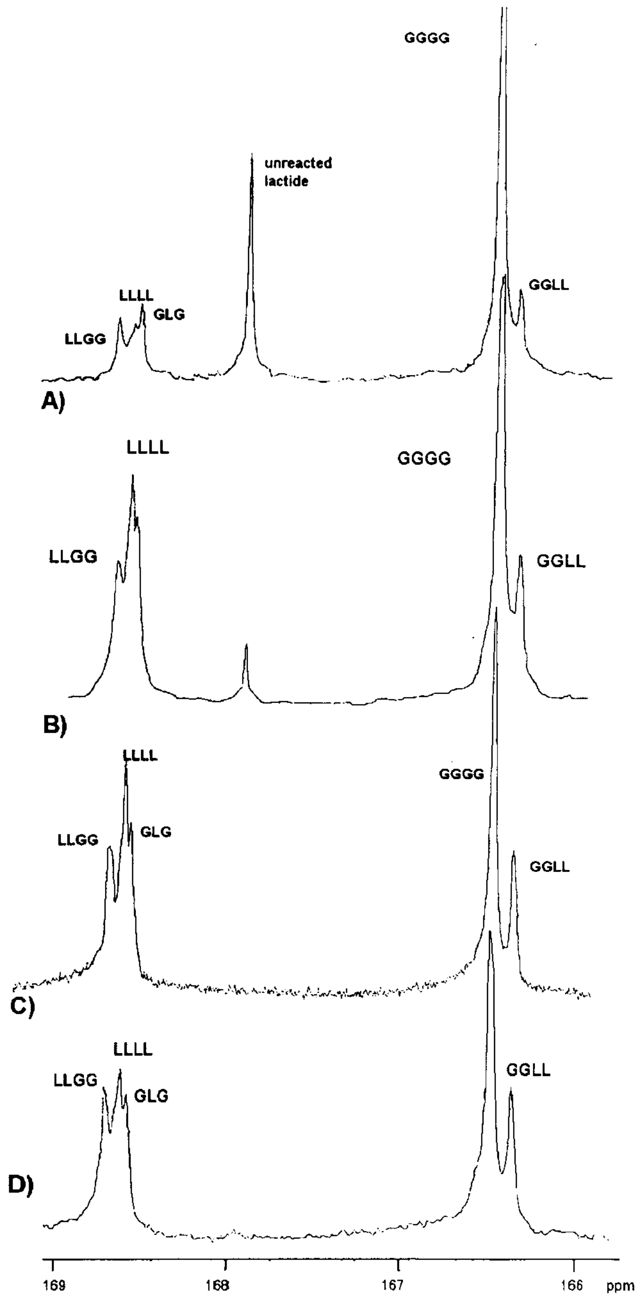

Figure 5. ^{13}C NMR spectra of poly(glycolide-*co*-L-lactide) (carbonyl region) obtained at different conversions: (A) conversion 41% (Table 2, position 2); (B) conversion 83% (Table 2, position 4); (C) conversion 100% (Table 2, position 6); (D) conversion 100% at 150 °C (Table 2, position 7A).

lactidyl block intermolecular transesterification of the second mode, was noticeable (Figure 2, signal 2). These results let us calculate coefficients of the second mode of glycolidyl sequences transesterification T_{II}(LGL) (Table 1). These values were lower than T_{II}(GLG).

These findings allowed us to assume that the chain of copolymers obtained by us at 100 °C had a more segmental structure than the structure of copolymers synthesized in copolymerization conducted with the use of tin initiators. Besides longer block structure made of glycolidyl and lactidyl microblocks, there were short alternative segments resulting from specific transesterification of the second mode. When the temperature of the reaction rises, the transestrification extent of lactidyl and glycolydyl blocks rises to the level achieved in reactions initiated by Sn(oct)$_2$ at 100 °C.

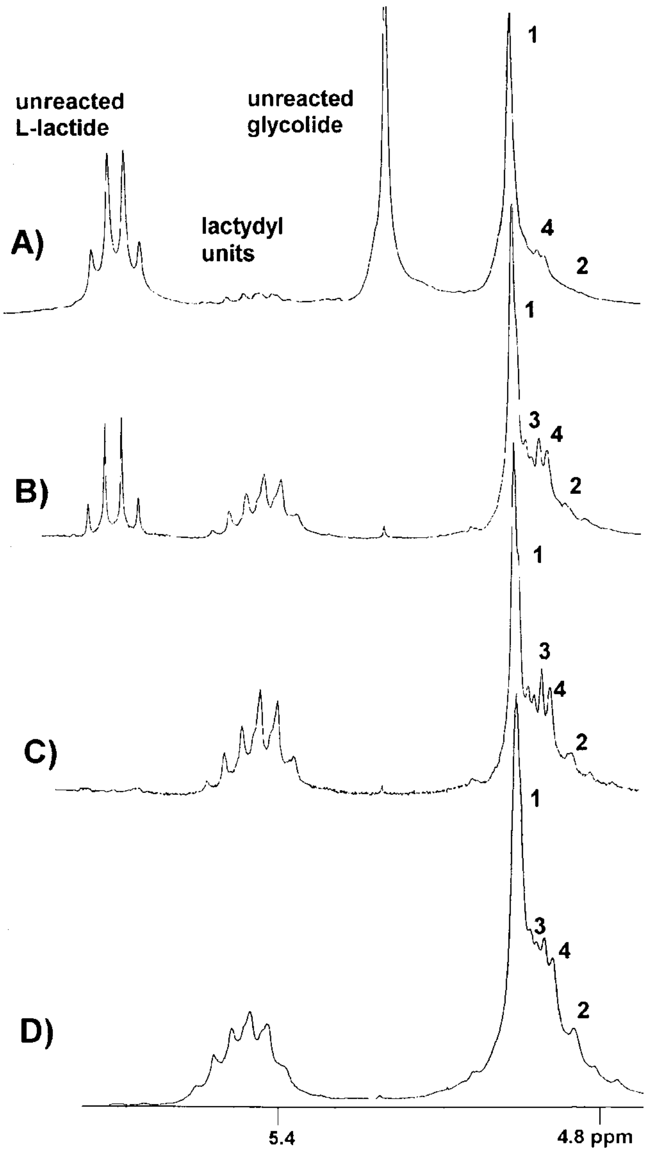

Figure 6. ^{1}H NMR spectra of poly(glycolide-*co*-L-lactide) obtained at different conversions: (A) conversion 41% (Table 2, position 2); (B) conversion 83% (Table 2, position 4); (C) conversion 100% (Table 2, position 6); (D) conversion 100% at 150 °C (Table 2, position 7A).

The spectra of copolymers, synthesized in the presence of tin octonate, showed the presence of analogues sequences as in copolymers obtained in the reactions initiated by Zr(acac)$_4$, however, with other quantitative relation (Figure 1, Figure 2). The average length of blocks, calculated on this basis, was shorter than length of copolymer blocks obtained in the presence Zr(acac)$_4$ at 100 °C. So, the extent of transesterification was greater.

2. Investigation of the Copolymerization Process. To explain the process of formation of the final microstructure of the obtained copolymer, the process of copolymerization and chain propagation was examined with the example of a equimolar copolymerization at temperatures of 100 and 150 °C.

Copolymerization of glycolide with L-lactide in the presence of Zr(acac)$_4$ was very fast (Figure 3), faster than the copolymerization with the use of Sn(oct)$_2$ at 220 °C described by Gilding.[5] Nevertheless, at the final stage of the reaction, its significant retardation was observed, particularly in the case of polymerization at

Table 2[a]

no.	initiator (temp)	time (h)	convn (%)	C_G (%)	C_L (%)	F_{GG} (%)	l_{GG}	l_{LL}	T_{II}[GLG]	T_{II}[LGL]
1	Zr(acac)$_4$ (100 °C)	0.25	18	33	1	92	8.3	0.7	≈10	0
2		0.5	41	54	20	73	6.0	2.2	4.1	0
3		4	71	94	50	69	4.6	2.1	2.0	0.2
4		8	83	98	70	58	4.4	3.2	0.6	0.5
5		24	91	≈100	84	54	4.3	3.8	0.6	0.5
6		120	≈100	≈100	≈100	50	4.0	4.0	1.1	0.5
1A	Zr(acac)$_4$ (150 °C)	0.03	30	40	10	75	6.5	1.9	11	0.4
2A		0.04	48	67	30	70	5.3	2.2	2.6	0.2
3A		0.17	65	90	36	66	4.5	2.3	2.3	0.2
4A		0.33	78	98	60	60	4.0	2.7	2.2	0.6
5A		1	85	99	74	58	3.8	2.8	1.4	0.9
6A		4	96	≈100	92	53	3.8	3.4	1.5	0.7
7A		24	≈100	≈100	≈100	50	3.5	3.5	1.4	0.8
8A		72	≈100	≈100	≈100	50	3.4	3.4	1.5	0.8

[a] Key: time, time of reaction; convn, total conversion of reaction; C_G, conversion of glycolide; C_L, conversion of L-lactide; F_{GG}, contents of glycolide in copolymer (mole percentage); l_{GG} or l_{LL}, average length of glycolidyl or lactydyl blocks in copolymer chains; T_{II}[GLG], yield of the second mode of transesterification (sequences GLG); T_{II}[LGL], yield of the second mode of transesterification (sequences LGL).

100 °C. It is apparently connected with the increase of the reaction medium viscosity—with the extent of the reaction.

Much higher reactivity of glycolide in comparison with lactide (Figure 4) was observed during the copolymerization. The reactivity of both comonomers was practically independent from the temperature of the copolymerization process (Figure 4). Thus, it was assumed that the differences of average microblock lengths for copolymers obtained in different temperatures (100 and 150 °C) were caused by various rate of transesterification in the copolymerization process. The values of reactivity coefficients of both comonomers at 150 °C were calculated with the use of an integrated form of the polymerization equation.[25,26] The calculations were carried out using the KyPlot Vers.2 program (author: Koichi Yoshioka; e-mail kyoshi@ja2.so-net.ne.jp) and were based on the data obtained for the amount of L-lactide in the copolymer higher than 25 mol %. Lower amounts of lactide in the copolymer may have caused larger NMR method-measuring errors concerning both the composition of the copolymer and the quantity of unreacted monomers in the reaction mixture. The following values of the activity coefficients were estimated: $r_G = 3.3$ and $r_L = 0.5$. They are comparable with analogous coefficients obtained by Gilding and Read for copolymerization initiated by Sn(oct)$_2$ ($r_G = 2.8$ and $r_L = 0.2$). Data describing the chain propagation process were presented in Table 2 and Figures 5 and 6. The chain propagation process was very similar for both examined temperatures. With the extent of reaction, a decrease of glycolidyl microblock average lengths was observed whereas average lengths of lactidyl blocks increased (Table 2, positions 2−6, 1A−7A). Long glycolidyl blocks were formed first of all during the initial phase of the reaction (Table 2, position 1, 1A, Figure 5). The recorded NMR spectra showed very strong bands characteristic for GGGG sequences (Figures 5A and 6A). The quantity of built-in lactide is small. The chain with glycolidyl active ends attacks scarce lactide, forming lactidyl groups, causing their transesterification to sequences containing lactyl groups. A very strong band characteristic for −GLG− groups in the spectrum ^{13}C NMR (Figure 5A) proves this fact. Moreover, it also proves the high extent of the second mode transesterification T_{II}[GLG] (Table 2, positions 1,1A). As a result of the processes, the initial structure of the chain comprised glycolidyl blocks separated by short lactyl and lactydyl groups. With the extent of the reaction, the glycolide concentration decreased and addition of lactide molecules to the growing chains were observed (Table 2, positions 3−6, 5A−8A, Figures 5 and 6). At this stage of the process, transesterification of glycolidyl groups was observed (−LGL− group appears in the spectrum—Figure 6, signal 2) which was caused by the increased concentration of active lactidyl ends of the chain (Table 2, Figure 5). The course of the reaction was shown in Figure 3. The increase of viscosity of the system caused the inhibition of the transesterification reaction, the main symptom of which was the lack of increase of transesterification coefficient for conversion higher than 80% (Table 2, positions 4−6, 5A−8A). When conversion of the reaction was close to 100% further heating did not cause visible progress of transesterification reaction (Table 2, positions 5, 6, and 7A, 8A).

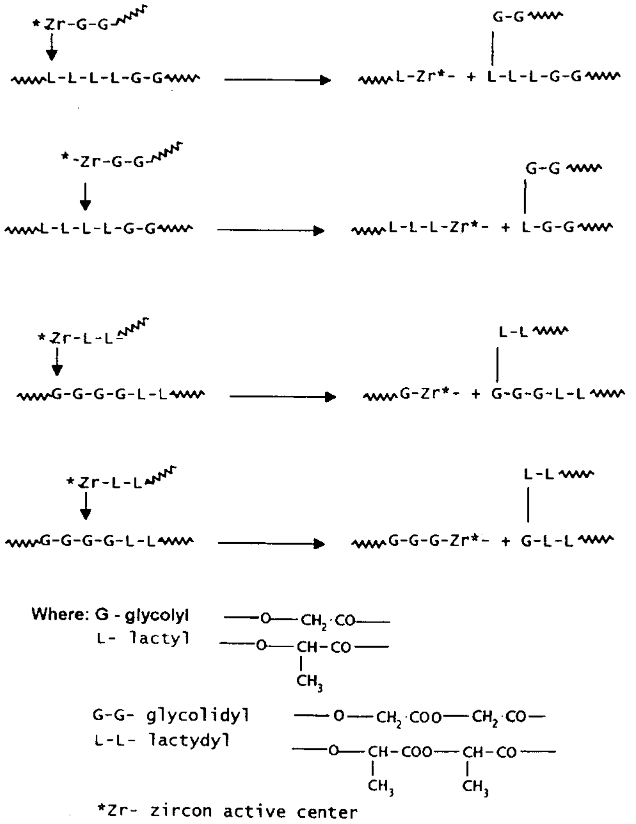

Figure 7. Scheme of the transesterification of the second mode occurring during the copolymerization.

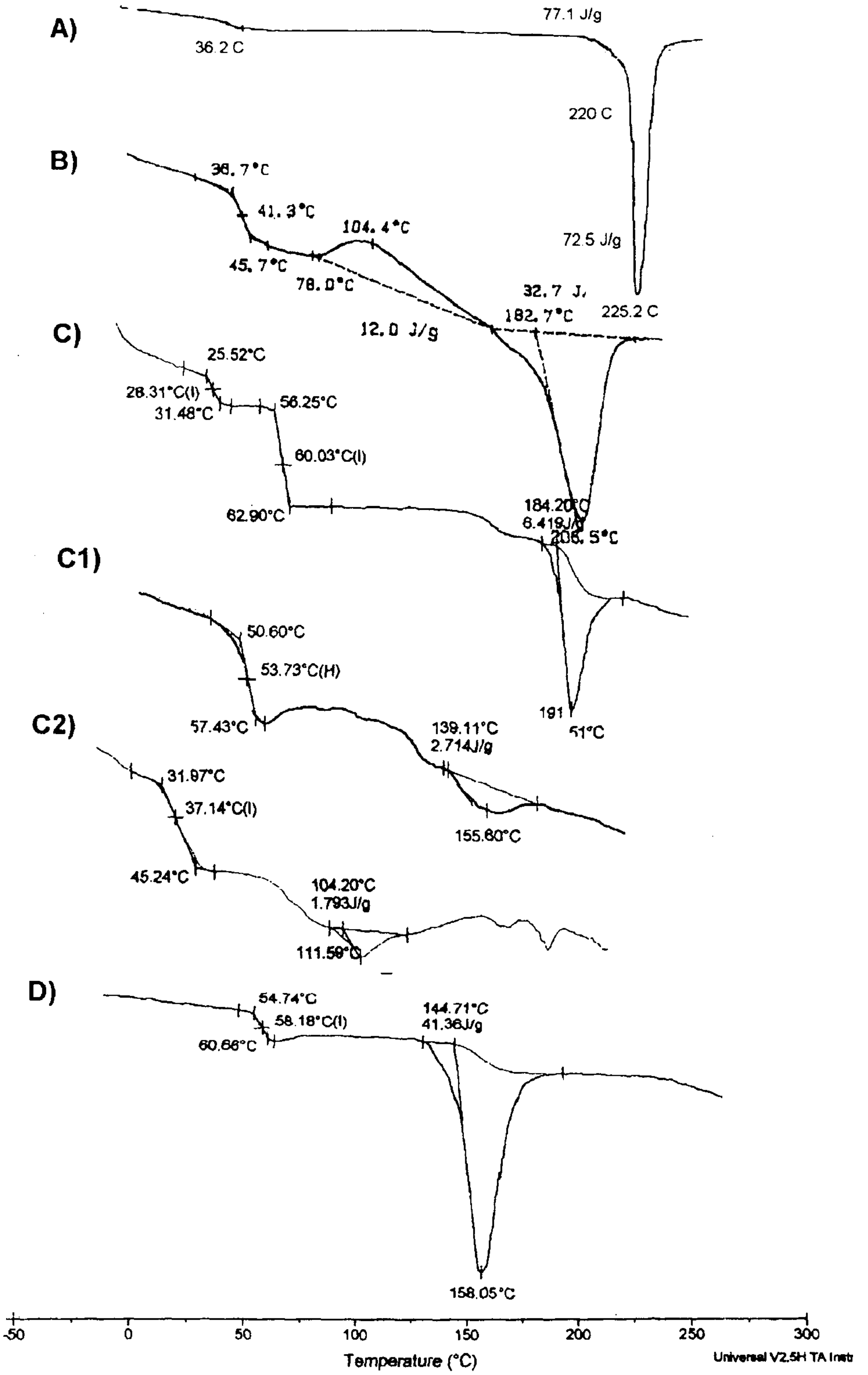

Figure 8. DSC thermograms (run I) of glycolide/lactide copolymers, obtained (A) at 150 °C polyglycolide, initiator Zr(acac)$_4$; (B) at 100 °C 80 mol % glycolide:20 mol % L-lactide, initiator Zr(acac)$_4$; (C) at 100 °C 50 mol % glycolide: 50 mol % L-lactide, initiator Zr(acac)$_4$; (C1) at 150 °C 50 mol % glycolide: 50 mol % L-lactide, initiator Zr(acac)$_4$; (C2) at 100 °C 50 mol % glycolide: 50 mol % L-lactide, initiator Sn(oct)$_2$; and (D) at 100 °C 15 mol % glycolide:85 mol % L-lactide, initiator Zr(acac)$_4$.

The findings showed that the final microstrusture of copolymer chain results from the reactivity of comonomers as well as transestrification processes taking place together with the main copolymerization reaction. Segmentality observed in chains of the obtained copolymers was caused by big differences between reactivities of glycolide and lactide and by transestrification, mainly the specific second mode transestrification of lactidyl groups (Figure 7), causing the appearance of short segments containing lactyl and glycolyl sequences (−GLG−, −LGL−, −GLGL−, and others similar to them). The difference between the structures of copolymers obtained in the presence of zirconium compounds and in the presence of tin compounds seems to result from the different extent of transesterification.

3. Properties of the Obtained Copolymers. To determine the utilization of the obtained copolymers, their properties and the influence of chain microstruc-

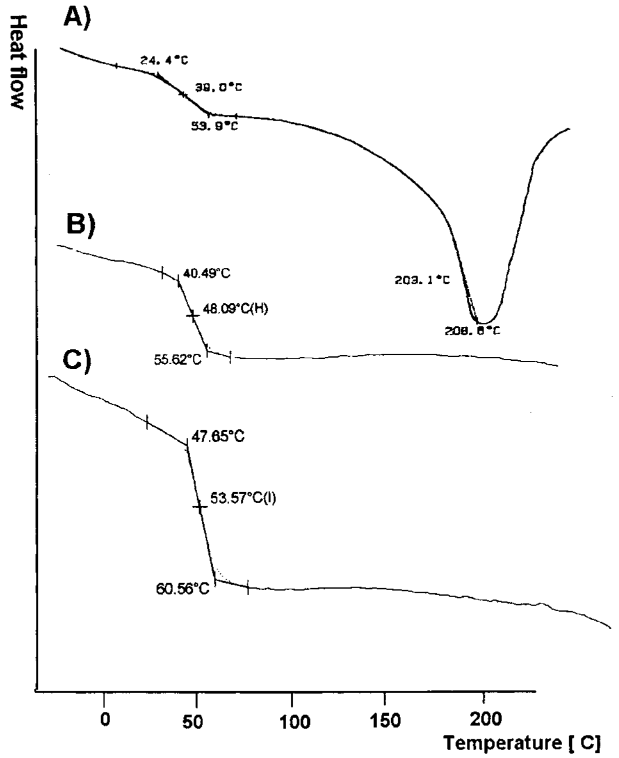

Figure 9. DSC thermograms (run II) of glycolide/lactide copolymers, obtained at 100 °C in the presence of $Zr(acac)_4$: (A) 80 mol % glycolide:20 mol % L-lactide; (B) 50 mol % glycolide:50 mol % L-lactide (C) 15 mol % glycolide:85 mol % L-lactide.

ture on these properties were examined. The results were compared with the ones estimated for the copolymers obtained by a $Sn(oct)_2$ initiator.

The results of DSC studies are presented in Figures 8 and 9 and Table 3. The thermogram of polyglycolide corresponded to the DSC traces of high molecular polyglycolide described by Cohn.[24] The lack of exotherm, which can be observed in the thermogram obtained by Gliding,[5] is a characteristic feature for polyglycolides of low molecular mass. The existence of a crystallization exotherm as well as of an endotherm connected with the melting of glycolidyl blocks crystalline phased was observed for copolymers containing 80 mol % of glycolide (Table 3 position 3, Figure 8B) The results were similar to the ones presented by Gilding for copolymers of analogous composition obtained in the presence of $Sn(oct)_2$.[5] However, big differences with respect to Gildings results were noticed for DSC thermograms (run I) of equimolar copolymers (Figure 8). The copolymer obtained with $Zr(acac)_4$ at 100 °C exhibited distinct melting endotherm of glycolidyl blocks crystalline phase. However, such an endotherm did not appear for the same copolymers synthesized at 150 °C as well as for copolymers obtained with $Sn(oct)_2$ (Figure 8C,C1,C2). This is in agreement with the data concerned with the microstructure of the tested copolymers (Table 1). Figure 9 shows thermograms of copolymers after melting and quick cooling of the sample at liquid nitrogen temperature (reheating—run II). In this case endotherm of crystallization was not observed for copolymers containing less than 80% glycolide. It is in accordance with previous examinations of copolymer morphology of glycolide with lactide, which showed that the rate of crystallization decreased with the contents of the lactide fraction in such copolymers.[27] Table 3 presents T_g and T_m, and crystalline phase melting heat values of the copolymers obtained with $Sn(oct)_2$ and $Zr(acac)_4$. The differeces in semicrystallinity, observed in run I, influenced the various T_g values obtained (Table 3, positions 4, 5, 6, 8, 9, and 11). Glass transition temperatures of amorphous samples obtained by quenching (II run) were similar to each other.

Some mechanical property tests were performed in order to check the utility of obtained copolymers as

Table 3[a]

			I run			II run		
no.	initiator (temp)	F_{GG} (%)	T_g (°C)	T_m (°C)	dH_t (J/g)	T_g (°C)	T_m (°C)	dH_t (J/g)
1	$Zr(acac)_4$ (150 °C)	100	39	225	75.6	36	225	82.0
2	$Sn(oct)_2$ (150 °C)	100	44	222	70.0	41	222	72.5
3	$Zr(acac)_4$ (100 °C)	82	41	206	32.7	39	208	39.1
4	$Zr(acac)_4$ (150 °C)	80	48	188	26.1	42		
5	$Sn(oct)_2$ (100 °C)	81	30	207	1.8	41	198	4.6
6	$Zr(acac)_4$ (100 °C)	50	60	192	6.4	48		
7	$Zr(acac)_4$ (150 °C)	50	53	139	2.7	47		
8	$Sn(oct)_2$ (100 °C)	50	37			45		
9	$Zr(acac)_4$ (100 °C)	15	58	158	41.4	54		
10	$Zr(acac)_4$ (150 °C)	15	63			52		
11	$Sn(oct)_2$ (100 °C)	15	38	170	20.5	34	163	27.2

[a] Key: F_{GG}, contents of glycolide in copolymer (mole percentage); T_g, glass transition temperature (°C); T_m, melt temperature; dH_t, heat of melting of crystalline phase.

Table 4[a]

no.	initiator (temp)	F_{GG} (%)	$M_v \times 10^{-3}$	$\sigma_{c_{max}}$ (MPa)	E_c (MPa)	σ_{max} (MPa)	E (MPa)	ϵ (%)	$T_{10\%}$ (°C)	T_{max} (°C)
1	$Zr(acac)_4$ (150 °C)	100	>40	110 ± 10	3100 ± 400				310	360
2	$Zr(acac)_4$ (100 °C)	82	277	85 ± 14	1200 ± 320	48 ± 6	3950 ± 760	1.0 ± 0.3	305	350
3	$Sn(oct)_2$ (100 °C)	81	119	58 ± 11	1600 ± 200	36 ± 4	3690 ± 410	1.1 ± 0.2	275	335
4	$Zr(acac)_4$ (100 °C)	50	154	47 ± 4	460 ± 67	39 ± 5	3320 ± 345	1.9 ± 0.2	290	345
5	$Sn(oct)_2$ (100 °C)	50	95	28 ± 3	490 ± 52	20 ± 4	2720 ± 210	2.8 ± 0.3	250	310
6	$Zr(acac)_4$ (100 °C)	15	110	102 ± 17	1060 ± 187	49 ± 6	2200 ± 143	1.1 ± 0.1	270	340
7	$Zr(acac)_4$ (150 °C)	15	103	93 ± 20	1155 ± 289	38 ± 8	2100 ± 139	1.2 ± 0.2	275	320

[a] Key: F_{GG}, feed mole fraction of glycolide (molar percentage); M_v, viscosity-average molecular weight; $\sigma_{c_{max}}$ and σ_{max}, maximum compression strength and tensile strength; E_c and E, shear modulus and Young's modulus; ϵ, elongation at break; $T_{10\%}$, T_{max} temperature of 10% weight loss, temperature of maximum weight loss.

materials for biodegradable bone implants. The results were compared with the properties of analogous copolymers obtained under the same conditions but during in copolymerization initiated by Sn(oct)$_2$. The results are presented in Table 4. The parameters describing mechanical properties of the synthesized copolymers were better than observed for analogous copolymers obtained with Sn(oct)$_2$ (Table 4 nos. 2,3 and 4,5). This was particularly evidently for equimolar copolymers, where the relative increases of compression and tensile strength were the largest. It corresponds to the more segmental structure of these copolymers. Similarly, higher resistance of the samples for thermal degradation was observed. It decreased with the increase of lactyde content in the copolymer. However, it was always higher than the thermal degradation temperature of the analogous copolymers obtained in the process of copolymerization initiated by Sn(oct)$_2$ (Table 4, nos. 2, 3 and nos. 4, 5). Better properties of the copolymers obtained with Zr(acac)$_4$ are probably connected with their specific microstructures. The results presented here showed that if the kind of initiator and the conditions of copolymerization are changed, it is possible to control to some extent the chain structure of the synthesized copolymer and at the same time its properties. Thus, we may be able to match the qualities of the obtained materials with the specific medical applications. Our results prove that glycolide copolymers with lactide obtained in reactions initiated by Zr(acac)$_4$ possess very good properties as material for biodegradable implants in medical applications because they do not contain toxic tin compounds.

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References and Notes

(1) Leenslang, J. W.; Pennings, A. J.;. Bos, R. M.; Rozema, F. R. *Biomaterials* **1987**, *8*, 70−76.

(2) Ikada, Y. In *Wound Close Biomaterials and Devices*; Chu, C.C., von Franhofer, L. A., Greisler, H. P., Eds.; CRC Press Inc.: Boca Raton, FL, Ann Arbor, MI, and London, 1992; pp 317−346.

(3) Thies, C. In *Microcapsules and Nanoparticicles in Medicine and Pharmacy*; Donbrow, M., Ed.; CRC Press: Boca Raton, FL, Ann Arbor, MI, and London, 1992; pp 47−71.

(4) Schmitt, E. E.; Epstein, M.; Polistina, R. A. U.S. Pat. 3 442 871, 1969.

(5) Gilding, D. K.; Reed, A. M. *Polymer* **1979**, *20*, 1459−1464.

(6) Schwach, G.; Coudane, J.; Engel, R.; Vert, M. *J. Polym. Sci., Part A* **1997,** *35*, 3431−3440.

(7) Levis, R. J. In *Sax's Dangerous Properties of Industrial Materials*, 8th ed.; Sr. Van Nostrand, Reinhold: New York, 1992.

(8) Kreiser-Saunders, I.; Kricheldorf, H. R. *Macromol. Chem. Phys.* **1998,** *199*, 1081−1087.

(9) Barskaja, I. G.; Ludvig, E. B.; Tarasov, S. G.; Godovsky, Jr. K. *Vysocomol. Soed*. **1983**, *25*, 1289−1294 (in Russian).

(10) Dobrzynski, P.; Kasperczyk, J.; Bero, M. *Macromolecules* **1999**, *32*, 4735−4737.

(11) Kricheldorf, H. R.; Berl, M.; Scharnagl, N. *Macromolecules* **1988**, *21*, 286−293.

(12) Miola-Delaite, Ch.; Hamaide, T.; Spitz, R. *Macromol. Chem. Phys.* **1999**, *200*, 1771−1778.

(13) Hayakawa, M.; Mitani, M.; Yamada, T.; Mukaiyama, T. *Macromol. Chem. Phys.* **1997**, *198*, 1305−1317.

(14) Salanki, Y.; D′eri, Y.; Platokhin, A. *Neurosci. Behav. Physiol.* **2000**, *30*, 63−73.

(15) Mattos, J. C.; Dantas, F. J.; Bezzera, R. J.; Bernardo-Filho, M.; Cabral-Neto, J. B. *Toxicol. Lett.* **2000**, *116*, 159−163.

(16) Bero, M.; Dobrzynski, P.; Kasperczyk, J. *Polym. Bull.* **1999**, *42*, 131−139.

(17) Kasperczyk, J. *Polymer* **1996**, 37 (2), 201−203.

(18) Penczek, S.; Duda, A.; Szymanski, R. *Macromol. Symp.* **1998**, *132*, 441−449.

(19) Kasperczyk, J.; Bero, M. *Makromol. Chem.* **1991**, *192*, 1777−1787.

(20) Kasperczyk, J.; Bero, M. *Makromol. Chem.* **1993**, *194*, 913−925.

(21) Chu, B. In *Comprehensive Polymer Science*; Booth, C., Price, C., Eds.; Pergamon Press: Oxford, England, 1989; Vol. 1, p 186.

(22) Kenley, R. A.; Lee, M. O.; Mahoney II, T. R.; Sanders, L. M. *Macromolecules* **1987,** *20*, 2398−2403.

(23) Schwarz, K.; Epple, M. *Makromol. Chem. Phys.* **1999**, *200*, 2221−2229.

(24) Cohn, D.; Younes, H.; Marom, G. *Polymer* **1987,** *28*, 2018−2022.

(25) Meyer, V. E.; Lovry, G. G. *J. Polym. Sci. Part A* **1965,** *3*, 2843−2851.

(26) Van den Brink, M.; Van Herk, M.; German, A. L. *J. Polym. Sci. Part A* **1999**, *37*, 3793−3803.

(27) Wang, Z. G.; Hsiao, B. S.; Zong, X. H.; Yeh, F.; Zhou, J. J.; Dormier, E.; Jamiolkowski, D. D. *Polymer* **2000**, *41*, 621−625.

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